Immune-Based Therapy Under Evaluation for Treatment of COVID-19

(Last updated May 12, 2020)

Summary Recommendations

There are no Food and Drug Administration-approved drugs for the treatment of COVID-19. Although reports have appeared in the medical literature and the lay press have claimed that patients with COVID-19 have been successfully treated with a variety of agents, definitive clinical trial data are needed to identify safe and effective treatments for this disease. Recommended clinical management of patients with COVID-19 includes infection prevention and control measures and supportive care, including supplemental oxygen and mechanical ventilatory support when indicated. As in the management of any disease, treatment decisions ultimately reside with the patient and their health care provider.
Immune-Based Therapy:
• There are insufficient data to recommend either for or against the use of **COVID-19 convalescent plasma** or **SARS-CoV-2 immune globulins** for the treatment of COVID-19 **(AIII)**.
• The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **non-SARS-CoV-2-specific intravenous immune globulin (IVIG)** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.
• There are insufficient data to recommend either for or against the use of the following agents for the treatment of COVID-19 **(AIII)**:
  • **Interleukin-1 inhibitors** (e.g., **anakinra**)
  • **Interleukin-6 inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**)
• Except in the context of a clinical trial, the Panel **recommends against** the use of other immunomodulators, such as:
  • **Interferons (AIII)**, because of the lack of efficacy in treatment of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) and toxicity.
  • **Janus kinase inhibitors** (e.g., **baricitinib**) **(AIII)**, because of their broad immunosuppressive effect.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional **Rating of Evidence:** I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

Several immune-based therapies that are directed at modifying the course of COVID-19 are currently under investigation or are being used off-label. These agents may target the virus (e.g., convalescent plasma) or modulate the immune response (e.g., interleukin-1 [IL-1] or interleukin-6 [IL-6] inhibitors).

For more information on host modifiers and immunotherapy that are under evaluation for COVID-19, see Tables 3a and 3b.

Interleukin-1 and Interleukin-6 Inhibitors and Other Immunomodulators

The cytokine profiles of serum from some patients with moderate to severe COVID-19 overlap with those seen in macrophage activation syndrome (MAS) and secondary hemophagocytic lymphohistiocytosis (sHLH).[1] MAS is characterized by hyperinflammation and manifests as fever, elevated ferritin levels, and pulmonary involvement, with a spectrum of presentation that includes sHLH.[2] Viruses are known triggers of MAS/sHLH, and high ferritin levels are associated with both MAS and mortality in patients with COVID-19.[3,4] Endogenous IL-1, a proinflammatory cytokine, potently induces IL-6 in monocytes and macrophages and is elevated in patients with COVID-19, MAS, and other conditions, such as severe chimeric antigen receptor T cell-mediated cytokine release syndrome.[5] The Janus kinase (JAK) family of enzymes regulate signal transduction in immune cells, and JAK inhibitors play a major role in inhibiting

and blocking cytokine release. IL-6 and IL-1 blockades and JAK inhibition, both of which have been proposed as an approach to treat the systemic inflammation associated with severe COVID-19 illness,[6] are reviewed in their respective pages.

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Convalescent Plasma and Immune Globulins

(Last updated May 12, 2020)

Recommendation:

- There are insufficient data to recommend either for or against the use of **COVID-19 convalescent plasma** or **SARS-CoV-2 immune globulins** for the treatment of COVID-19 **(AIII)**.

Rationale for Recommendation

Although convalescent plasma and virus-specific immune globulin have been used for other viral infections, sufficient clinical data are lacking for COVID-19, and potential risks include transfusion reactions. Theoretical risks include antibody-dependent enhancement of infection.

Rationale for Use in Patients with COVID-19

Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2,[1] and SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.

Clinical Data for COVID-19

Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports.[1-6] There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in patients with COVID-19.

Clinical Data for Other Viral Infections

The use of convalescent plasma has been evaluated for other viral diseases, such as severe acute respiratory syndrome (SARS), with some suggestion of potential benefit.[7-9] However, no convalescent blood products are currently licensed by the Food and Drug Administration (FDA).

There are no clinical data on the use of specific immune globulin or hyperimmune globulin products in patients with SARS or Middle East respiratory syndrome (MERS).

Several virus-specific immune globulin products are licensed for preventing post-transplant cytomegalovirus (CMV) disease (CytoGam) and post-exposure prophylaxis of varicella in high-risk individuals (VariZig).

Clinical Trials and Access

Randomized clinical trials to evaluate convalescent plasma for the treatment of COVID-19 are underway; a list is available at *ClinicalTrials.gov*. Trials evaluating SARS-CoV-2 immune globulins are in development.

The FDA has provided guidance for the use of COVID-19 convalescent plasma under an Emergency Investigational New Drug Application. The FDA has also approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information. People who have been fully recovered from COVID-19 for at least two weeks and who are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the American Red Cross website.

Adverse Effects

The risks associated with plasma transfusion include antibody-mediated enhancement of infection, transfusion-associated acute lung injury, transfusion-associated circulatory overload, and allergic transfusion reactions.[3,10] Rare complications include the transmission of infectious pathogens and red cell alloimmunization.

Considerations in Pregnancy

Pathogen-specific immune globulins are used clinically during pregnancy to prevent varicella zoster virus (VZV) and rabies and have also been used in clinical trials of therapies for congenital CMV infection.

Considerations in Children

Hyperimmune globulin has been used to treat several viral infections in children, including VZV, respiratory syncytial virus, and CMV; efficacy data for other respiratory viruses is limited. The efficacy and adverse effects associated with administration of convalescent plasma have not been well established.

Non-SARS-CoV-2-Specific Intravenous Immune Globulin

Recommendation:

- The COVID-19 Treatment Guidelines Panel **recommends against** the use of **non-SARS-CoV-2-specific intravenous immune globulin (IVIG)** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**. This should not preclude the use of IVIG when it is otherwise indicated for the treatment of complications that arise during the course of COVID-19.

Rationale for Recommendation

Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors who were not confirmed to have had SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.

Clinical Data for COVID-19

These data have not been peer reviewed.

In a retrospective, non-randomized cohort study of IVIG in eight treatment centers in China between December 2019 and March 2020, the authors found no difference in 28-day or 60-day mortality between the 174 patients who were treated with IVIG and the 151 patients who were not treated with IVIG.[1] Patients who received IVIG were hospitalized for a longer period (median of 24 days vs. 16 days) and experienced longer duration of disease (median of 31 days vs. 23 days). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 patients [41%] with critical status in the IVIG group vs. 32 [21%] in the non-IVIG group). A subgroup analysis that was limited to the critical patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days.

The results of this study are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG or no IVIG, and the IVIG group was older, was more likely to have coronary heart disease, and had a higher proportion of patients with severe COVID-19 disease at study entry. Patients also received numerous other concomitant therapies for COVID-19.

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Interleukin-1 Inhibitors

(Last updated June 11, 2020)

Recommendation

- There are insufficient data to recommend either for or against the use of **interleukin-1 (IL-1) inhibitors**, such as **anakinra**, for the treatment of COVID-19.

Rationale

There are no data from clinical trials on the use of IL-1 inhibitors in patients with COVID-19.

Anakinra is a recombinant human IL-1 receptor antagonist. It is approved to treat rheumatoid arthritis and cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease.[1] It is also used off-label for severe chimeric antigen receptor T cell (CAR T-cell)-mediated cytokine release syndrome (CRS) and macrophage activation syndrome (MAS)/secondary hemophagocytic lymphohistiocytosis.

Rationale for Use in Patients with COVID-19

Endogenous IL-1 is elevated in patients with COVID-19 and other conditions, such as severe CAR-T-cell mediated CRS. There are case reports and series that describe a favorable response with anakinra in these syndromes, including survival benefit in sepsis and reversing cytokine storm in adults with MAS after tocilizumab failure.[2,3]

Clinical Data for COVID-19

- A single-center case series reported outcomes following the open-label use of anakinra in nine hospitalized patients with COVID-19 who presented with 4 to 12 days of symptoms, required oxygen ≤6 liters/minute, and had serum C-reactive protein (CRP) ≥50 mg/L. Anakinra 100 mg was administered subcutaneously (SQ) every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two of the nine patients also received hydroxychloroquine plus azithromycin; the other seven patients received no specific treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after receiving the first dose of the drug. Data regarding the other eight patients indicated good clinical outcomes as assessed by oxygen flow, decline in CRP levels, and serial computerized tomography (CT) scans that showed no progression in infiltrates. By Day 11, none of the patients had died. Three patients experienced liver transaminase levels ≥3 times the upper limit of normal. However, the study results are difficult to interpret because of the low number of patients included in the case series and the absence of a comparison group.[4]
- A single-center retrospective cohort study compared outcomes in 29 patients following open-label use of anakinra to outcomes in 16 historical controls enrolled at the same center in Italy. All patients had COVID-19, moderate to severe acute respiratory distress syndrome (ARDS) that required non-invasive ventilation, and evidence of hyperinflammation (CRP ≥100 mg/L and/or ferritin ≥900 ng/mL). High-dose intravenous (IV) anakinra 5 mg/kg twice daily (the IV formulation is not approved in the United States) was administered for a median of 9 days, followed by SQ administration of anakinra 100 mg twice daily for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received hydroxychloroquine and lopinavir/ritonavir. In the anakinra group, reductions in CRP levels were noted over several days following anakinra initiation and the 21-day survival rate was higher in the anakinra group than in the control group (90% vs. 56%, $P = 0.009$). However, the median age in the anakinra group was younger than in the control

group (median 62 years vs. 70 years), and a smaller percentage of patients in the anakinra group had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) because of adverse events (four patients developed bacteremia and three patients had elevated liver enzymes); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of seven patients received low-dose SQ anakinra 100 mg twice daily; however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.[5]

Clinical Trials

A number of clinical trials for the treatment of COVID-19 are currently underway (a list of clinical trials is available here: Anakinra.

Adverse Effects

Anakinra was not associated with any significant safety concerns in trials of sepsis.[6-8] Increased rates of infection were reported with prolonged use in combination with tumor necrosis factor-alfa blockade, but not with short-term use.[9]

Considerations in Pregnancy

There is limited evidence on which to base a recommendation in pregnancy, but unintentional first trimester exposure is unlikely to be harmful.[10]

Considerations in Children

Anakinra has been used extensively in the treatment of severely ill children with complications of rheumatologic conditions, including MAS. Pediatric data on the use of anakinra in ARDS/sepsis are limited.

Drug Availability

Procuring anakinra may be a challenge at some hospitals in the United States. Anakinra is approved only in an SQ formulation.

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Interleukin-6 Inhibitors

(Last updated June 11, 2020)

Recommendation

- There are insufficient data to recommend either for or against the use of **interleukin-6 (IL-6) inhibitors** (e.g., **sarilumab**, **siltuximab**, **tocilizumab**) for the treatment of COVID-19.

Rationale

There are insufficient data from clinical trials on the use of IL-6 inhibitors in patients with COVID-19.

Rationale for Use in Patients with COVID-19

IL-6 is a pleiotropic, pro-inflammatory cytokine produced by a variety of cell types, including lymphocytes, monocytes, and fibroblasts. Infection by the related SARS-associated coronavirus induces a dose-dependent production of IL-6 from bronchial epithelial cells.[1] Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. COVID-19-associated systemic inflammation and hypoxic respiratory failure is associated with heightened cytokine release, as indicated by elevated blood levels of IL-6, C-reactive protein (CRP), D-dimer, and ferritin.[2-4]

Sarilumab

Sarilumab is a recombinant humanized anti-interleukin-6 receptor (IL-6R) monoclonal antibody that is approved by the Food and Drug Administration (FDA) for use in patients with rheumatoid arthritis. It is available as a subcutaneous (SQ) formulation and is not approved for cytokine release syndrome (CRS). A placebo-controlled clinical trial is evaluating the use of an intravenous (IV) formulation administered as a single dose for COVID-19.

Clinical Data for COVID-19

Press Release, April 27, 2020: In a Phase 2/3 clinical trial (*ClinicalTrials.gov* identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an Independent Data Monitoring Committee recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. At the time of the interim review of the first 457 participants enrolled, 145 were randomized to receive sarilumab 400 mg, 136 to receive sarilumab 200 mg, and 77 to receive placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction.[5]

Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (this is the primary outcome measure of the Phase 2 trial).

At the time of data analysis, the percentage of patients with critical illness (n = 226) who died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%). Comparing mortality alone, the percentage of patients who died also was lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among patients with critical illness who received sarilumab, the April 27, 2020, press release about the study cited "negative trends" for most outcomes in patients with severe illness who received the drug.

Adverse Effects

The primary lab abnormalities that have been reported with sarilumab treatment are transient and/or reversible elevations in liver enzymes that appear to be dose dependent and rare occurrences of neutropenia and thrombocytopenia. Risk for serious infections (e.g., tuberculosis [TB], other bacterial pathogens) have been reported only in the context of long-term use of sarilumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Availability

The SQ formulation of sarilumab is not approved for CRS. The IV formulation is not approved by the FDA, but it is being studied in a clinical trial of hospitalized patients with COVID-19. A list of current clinical trials is available at *ClinicalTrials.gov*.

Siltuximab

Siltuximab is a recombinant human-mouse chimeric monoclonal antibody that binds IL-6 and that is approved by the FDA for use in patients with Castleman's disease. Siltuximab prevents the binding of IL-6 to both soluble and membrane-bound IL-6R, inhibiting IL-6 signaling. Siltuximab is dosed as an IV infusion.

Clinical Data in COVID-19

There are limited, unpublished data describing the efficacy of siltuximab in patients with COVID-19.[6] There are no data describing clinical experiences using siltuximab for patients with other novel coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome.

Clinical Trials

See *ClinicalTrials.gov* for a list of current clinical trials for siltuximab and COVID-19.

Adverse Effects

The primary adverse effects (AEs) reported for siltuximab have been related to rash. Additional AEs, such as serious bacterial infections, have been reported only in the context of long-term dosing of siltuximab once every 3 weeks.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Drug Availability

Procuring siltuximab may be a challenge at some hospitals in the United States.

Tocilizumab

Tocilizumab is a recombinant humanized anti-IL-6R monoclonal antibody that is approved by the FDA for use in patients with rheumatologic disorders and CRS induced by chimeric antigen receptor T cell (CAR-T) therapy. Tocilizumab can be dosed for IV or SQ injection. For CRS, the IV formulation should be used.[7]

Clinical Data for COVID-19

- *Press Release, April 27, 2020:* The CORIMUNO-TOCI trial (*ClinicalTrials.gov* identifier NCT04331808) is an open-label, randomized trial of hospitalized patients with COVID-19 (n = 129 at seven sites in France) who had moderate or severe disease at study entry and who were randomized to receive tocilizumab plus standard of care (n = 65) or standard of care alone (n = 64). Patients received tocilizumab 8 mg/kg on Day 1. If there was no response to the treatment (i.e., no decrease in oxygen requirement), a second infusion of tocilizumab was administered on Day 3. In this preliminary report, the proportion of participants who had died or who needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the standard of care group. Detailed results of the trial have not been reported. The Data and Safety Monitoring Board resigned after the press release was issued.[8]
- *Published study:* Sixty-three hospitalized adult patients with COVID-19 were enrolled in a prospective, open-label study of tocilizumab for severe COVID-19. Criteria for inclusion in the study were polymerase chain reaction-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection; pulmonary involvement, assessed either by oxygen saturation ($Sa0_2$) <93% on room air or PaO_2/FiO_2 ratio <300 mm Hg; and at least three of the following: CRP >10 times normal values, ferritin >1,000 ng/mL, D-dimer >10 times normal values, or lactate dehydrogenase >2 times the upper level of normal. The patients' mean age was 62.6 years and most (88%) were male; 39.7% of the patients were febrile, and 95.7% had bilateral pulmonary infiltrates. Five patients were on mechanical ventilation at baseline. All of the patients received off-label antiretroviral protease inhibitors. Patients received either tocilizumab IV (8 mg/kg) or tocilizumab SQ (324 mg); within 24 hours after this initial dose, a second dose was administered to 52 of the 63 patients. Following administration of tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The mean PaO_2/FiO_2 ratio of the patients increased between admission (152 +/- 53 mm Hg) and Day 7 of hospitalization (284 +/- 116 mm Hg). No moderate or severe adverse events attributable to tocilizumab were reported. The overall mortality rate was 11% (7 of 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association between earlier use of tocilizumab and reduced mortality; however, interpretation of this result is limited because the study results did not describe a comparison group or specify an a priori comparison.[9]

Clinical Trials

See *ClinicalTrials.gov* for ongoing trials that are evaluating the use of tocilizumab for the treatment of COVID-19.

Adverse Effects

The primary laboratory abnormalities reported with tocilizumab treatment are elevated liver enzyme levels that appear to be dose dependent. Neutropenia or thrombocytopenia are uncommon. Additional AEs, such as risk for serious infections (e.g., TB, other bacterial pathogens), have been reported only in the context of continuous dosing of tocilizumab.

Considerations in Pregnancy

There are insufficient data to determine whether there is a drug-associated risk for major birth defects or miscarriage. Monoclonal antibodies are actively transported across the placenta as pregnancy progresses (with greatest transfer during the third trimester) and may affect immune responses *in utero* in the exposed fetus.

Considerations in Children

In children, tocilizumab is frequently used for CRS following CAR-T therapy[10] and it is occasionally used for MAS.[11] Pediatric data for its use in ARDS/sepsis are limited.

Drug Availability

Procuring IV tocilizumab may be a challenge at some hospitals in the United States.

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Other Immunomodulators

(Last updated May 12, 2020)

Interferons (Alfa, Beta)

Recommendation:

- The COVID-19 Treatment Guidelines Panel (the Panel) **recommends against** the use of **interferons** for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Rationale for Recommendation

Studies have shown that there was no benefit when interferons were used in patients with other coronavirus infections (i.e., severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and the significant toxicities of interferons outweigh the potential for benefit. In addition, there is a lack of clinical trial results for patients with COVID-19.

Rationale for Use in Patients with COVID-19

Interferons, a family of cytokines with antiviral properties, have been suggested as a potential treatment for COVID-19 because of their *in vitro* and *in vivo* antiviral properties.

Clinical Data for COVID-19

Interferon-beta used alone and in combination with ribavirin in patients with SARS and MERS has failed to show a significant positive effect on clinical outcomes.[1-5]

In a retrospective observational analysis of 350 critically ill patients with MERS[2] from 14 hospitals in Saudi Arabia, mortality rates were higher among patients who received ribavirin and interferon (beta-1a, alfa-2a, or alfa-2b) than among those who did not receive either drug.

A randomized clinical trial that included 301 patients with acute respiratory distress syndrome[6] found that, compared to placebo, intravenous interferon beta-1a had no benefit as measured by ventilator-free days over a 28-day period (median of 10.0 days vs. 8.5 days) or mortality (26.4% vs. 23.0%).

Interferon-alfa-1b, which is not available in the United States, has been used in patients with COVID-19 in China, but it has been primarily used by atomization inhalation, and the clinical data have not yet been presented.

Adverse Effects

The most frequent adverse effects of interferon-alfa include flu-like symptoms, nausea, fatigue, weight loss, hematological toxicities (cytopenias), elevated transaminases, and psychiatric problems (depression and suicidal ideation). Interferon-beta is better tolerated than interferon-alfa.

Drug-Drug Interactions

The most serious interactions with interferons are the potential for added toxicity with other immunomodulators and chemotherapeutic agents.

Considerations in Pregnancy

Data from several large pregnancy registries did not demonstrate an association between exposure to interferon-beta-1b preconception or during pregnancy and an increased risk of adverse birth outcomes

(e.g., spontaneous abortion, congenital anomaly), and exposure did not influence birth weight, height, or head circumference.

Considerations in Children

There are limited data on the use of interferons for the treatment of respiratory viral infections in children.

Janus Kinase Inhibitors (e.g., Baricitinib)

Recommendation:

- The Panel **recommends against** the use of **Janus kinase (JAK) inhibitors** (e.g., **baricitinib**) for the treatment of COVID-19, except in the context of a clinical trial **(AIII)**.

Rationale for Recommendation

At present, the broad immunosuppressive effect of JAK inhibitors outweighs the potential for benefit.

Baricitinib is an oral JAK inhibitor that works by inhibiting the JAK signal transducer and activator of transcription pathway. Baricitinib is approved by the Food and Drug Administration to treat rheumatoid arthritis and can ameliorate the chronic inflammation seen in interferonopathies.[7-9]

Rationale for Use in Patients with COVID-19

Baricitinib is a potent anti-inflammatory with activity against interferon-associated inflammation. It has also been postulated to have an antiviral effect. A related drug, ibrutinib, has been shown to decrease lung inflammation in a mouse model of influenza.[10,11]

Clinical Data for COVID-19

No clinical data has been reported to date.

Adverse Effects

Side effects have been observed with prolonged use, including upper respiratory infections (>10% of patients), increased levels of low-density lipoproteins, herpesvirus infections, increased liver function test levels, and thrombocytosis.

Considerations in Pregnancy

In animal studies of embryo-fetal development, there was increased embryo lethality in some species that were given baricitinib at very high doses, well above the recommended dose for humans.[12] The limited human data on the use of baricitinib are insufficient to evaluate the drug-associated risk for major birth defects or miscarriage.[12]

Corticosteroids

The role of corticosteroids as concomitant therapy in persons with COVID-19 is discussed in Considerations for Certain Concomitant Medications in Patients with COVID-19.

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Table 3a. Immune-Based Therapy Under Evaluation for Treatment of COVID-19: Clinical Data to Date

(Last updated June 11, 2020)

Information presented in this table may include data from pre-print/non-peer reviewed articles. This table will be updated as new information becomes available.

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Blood Products			
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Not approved by the FDA	Plasma donated from individuals who have recovered from COVID-19 includes antibodies to SARS-CoV-2.[1] Similarly, SARS-CoV-2 immune globulin is a concentrated antibody preparation derived from the plasma of people who have recovered from COVID-19. Both products may help suppress the virus and modify the inflammatory response.	**For COVID-19:** • Data supporting the use of convalescent plasma for COVID-19 are limited to a small retrospective cohort study, small case series, and case reports. • There are no clinical data on the use of SARS-CoV-2 immune globulin or hyperimmune globulin in COVID-19. **For Other Viruses:** • The use of convalescent plasma has been evaluated in other viral diseases (e.g., SARS), with some suggestion of potential benefit.[2-9] No convalescent blood products are currently licensed by the FDA. • There are no clinical data on the use of specific immune globulin or hyperimmune globulin in patients with SARS or MERS.
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	• Primary immune disorders • Thrombocytopenic purpura • Kawasaki disease • Motor neuropathy • Prophylaxis of various bacterial and viral infections	• Passive immunity; human immunoglobulin is derived from pooled plasma of blood donors and contains antibodies against a broad spectrum of pathogens. • Currently, only a small proportion of the U.S. population has been infected with SARS-CoV-2. Therefore, products derived from the plasma of donors who were not confirmed to have had SARS-CoV-2 infection are not likely to contain SARS-CoV-2 antibodies.	**For COVID-19** • *Not Peer Reviewed:* A retrospective, nonrandomized cohort study of IVIG in eight treatment centers in China between December 2019 and March 2020 found no difference in 28-day or 60-day mortality between the 174 patients who were treated with IVIG and the 151 patients who were not treated with IVIG. Patients who received IVIG were hospitalized for longer (median of 24 days vs. 16 days) and experienced longer duration of disease (median of 31 days vs. 23 days). It should be noted that a higher proportion of IVIG-treated patients had severe disease at study entry (71 [41%] with critical status in the IVIG group vs. 32 [21%] in the non-IVIG group). A subgroup analysis that was limited to the critical patients suggested a mortality benefit at 28 days, which was no longer significant at 60 days. The results are difficult to interpret because of important limitations in the study design. In particular, patients were not randomized to receive IVIG versus no IVIG, and in the IVIG group, the patients were older and more likely to have coronary heart disease, and at study entry, the proportion of patients with severe COVID-19 disease was higher. Also, patients received numerous other concomitant therapies for COVID-19.[10]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interferon Alfa and Interferon Beta			
Interferon Alfa and Interferon Beta	• IFN alfa-2b: Leukemia, melanoma, lymphoma, condylomata acuminata, Kaposi sarcoma, hepatitis B, hepatitis C • IFN alfa-1b is not available in the United States	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types[11-13]	No clinical data for COVID-19. **For MERS:**[14-17] • Retrospective studies with IFN alfa-2a, IFN alfa-2b, or IFN beta-1a in combination with ribavirin showed no clear benefit. • Ribavirin plus IFN alfa-2a survival rates: 30% to 100% in three small studies (n < 20)[18] • Ribavirin plus IFN alfa-2a or IFN alfa-2b: No significant improvement in clinical outcome or survival at 28 days.[19] • Ribavirin plus IFN beta-1a SQ: Retrospective analyses showed no significant effect on clinical outcome.[14] **Inhaled IFN beta-1a (SNG001):** • Phase 2 clinical trials showed improved lung function in asthma patients with respiratory infections.[20]
	• Multiple sclerosis (IFN beta-1a, IFN beta-1b)	• Elicits antiviral, antiproliferative, and immunomodulatory activities on numerous cell types (T cell, B cell, and cytokine function)[11,21] • Among IFN subtypes, IFN beta-1b shows greatest *in vitro* inhibition of MERS-CoV.[16,22] • *In vitro* activity against MERS-CoV in lung cells.[20]	
Interleukin-1 Inhibitor			
Anakinra	• Rheumatoid arthritis • Cryopyrin-associated periodic syndromes, specifically neonatal-onset multisystem inflammatory disease[23]	Competitively inhibits IL-1 binding to the IL-1 type I receptor	**For COVID-19** • A single-center case series reported on open-label use of anakinra in nine hospitalized patients with COVID-19, presenting with 4 days to 12 days of symptoms, requiring oxygen ≤6 L/minute, and serum CRP ≥50 mg/L. Anakinra was administered SQ, 100 mg every 12 hours for 3 days followed by 100 mg daily for up to 7 more days. Two of the nine patients also received HCQ plus AZM; the other 7 patients received no specific treatments. Anakinra was discontinued in one patient who progressed to acute respiratory failure after the first dose of the drug. Good clinical outcomes were observed in the other eight patients as assessed by oxygen flow, decline in CRP, and no progression in infiltrates on serial CT scans. Three patients experienced elevated liver transaminase levels. Results are difficult to interpret because of the low number of patients in the case series, the short follow-up, and the absence of a comparison group.[24]

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Interleukin-1 Inhibitor, continued			
Anakinra, continued			• A single-center retrospective cohort study in Italy compared outcomes in 29 patients following open-label anakinra use to outcomes in 16 historical controls. All patients had COVID-19 with moderate to severe ARDS requiring non-invasive ventilation, and evidence of hyperinflammation. High-dose IV anakinra 5 mg/kg twice daily (IV formulation is not approved in the United States) was administered for a median of 9 days, followed by SQ administration (anakinra 100 mg twice daily) for 3 days to avoid inflammatory relapses. Both the anakinra and control (standard treatment) groups received HCQ and LPV/r. In the high-dose anakinra group, reductions in CRP levels were noted following anakinra initiation. The 21-day survival was 90% in the anakinra group and 56% in the control group (P = 0.009); however, the patients in the anakinra group were younger (median 62 years vs. 70 years), and fewer had chronic kidney disease. High-dose anakinra was discontinued in seven patients (24%) due to AEs (bacteremia in four patients, elevated liver enzymes in three patients); however, retrospective assessment showed that these events occurred with similar frequency in the control group. An additional group of seven patients received low-dose SQ anakinra (100 mg twice daily); however, treatment in this group was stopped after 7 days because of lack of clinical or anti-inflammatory effects.[25]
Interleukin-6 Inhibitors Elevations in IL-6 levels may be an important mediator when severe systemic inflammatory responses occur in some patients with COVID-19; IL-6 inhibition may reduce these effects.			
Sarilumab	Rheumatoid arthritis[26]	• Human recombinant monoclonal antibody • IL-6 receptor antagonist	**For COVID-19** • *Press Release:* In a Phase 2/3 clinical trial (*ClinicalTrials.gov* Identifier NCT04315298), hospitalized COVID-19 patients were randomized (2:2:1) to receive sarilumab 400 mg, sarilumab 200 mg, or placebo. Preliminary data were released after an IDMC recommended discontinuing the 200-mg arm and restricting future enrollment to critical patients only. Of the first 457 participants enrolled, 145 were randomized to sarilumab 400 mg, 136 to sarilumab 200 mg, and 77 to placebo. At study entry, 28% of the patients had severe illness, 49% had critical illness, and 23% had multisystem organ dysfunction. Sarilumab decreased CRP, which changed by -79%, -77%, and -21% in the sarilumab 400 mg group, sarilumab 200 mg group, and placebo group, respectively (primary outcome of the Phase 2 trial). At the time of data analysis, of the 226 critical patients, the proportion of patients who had died or were on a ventilator was lower in the sarilumab 400 mg group (28%) than in the sarilumab 200 mg group (46%) and in the placebo group (55%).

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on *ClinicalTrials.gov*)
Interleukin-6 Inhibitors, continued			
Sarilumab, continued			Comparing mortality alone, the proportion of patients who died was also lower in the sarilumab 400 mg group (23%) than in the sarilumab 200 mg group (36%) and in the placebo group (27%). In contrast to the positive trend in outcomes among the critical patients, the press release cited "negative trends" for most outcomes in severe patients who received sarilumab.[28]
Siltuximab	Multicentric Castleman disease	• Human-mouse chimeric monoclonal antibody • IL-6 antagonist[29]	**For COVID-19** • *Not Peer Reviewed:* In a single-center observational study of 21 patients with COVID-19 who developed pneumonia/ARDS and received treatment with IV siltuximab, some patients experienced decreased CRP levels (16 of 21 patients) and improved clinical condition (seven of 21 patients) following siltuximab treatment. Other patients experienced no clinically relevant change in condition (nine of 21 patients) or worsening condition (five of 21 patients). Among the five patients with worsening condition, there was one death and one cerebrovascular event (median follow-up of 8 days).[30]
Tocilizumab	• Cytokine release syndrome (induced by CAR T-cell therapy) • Rheumatoid arthritis • Giant cell arteritis • Polyarticular juvenile idiopathic arthritis • Systemic juvenile idiopathic arthritis[31]	• Recombinant humanized monoclonal antibody • IL-6 receptor antagonist	**For COVID-19** • *Press Release:* Early results were reported for the CORIMUNO-TOCI trial (*ClinicalTrials.gov* Identifier NCT04331808), an open-label randomized trial of hospitalized patients with COVID-19 (n = 129) at seven sites in France. The patients, who had moderate or severe disease at study entry, were randomized to receive tocilizumab plus SOC (n = 65) or SOC alone (n = 64). The dosing strategy was tocilizumab 8 mg/kg on Day 1; if there was no response (i.e., no decrease of oxygen requirement), a second infusion was repeated on Day 3. In this preliminary report, the proportion of participants who died or needed ventilation (noninvasive or mechanical) was lower in the tocilizumab group than in the SOC alone group. Detailed results of the trial have not been reported. • 63 hospitalized adult patients were enrolled in a prospective open-label study of tocilizumab for severe COVID-19. All patients received off-label ARV PIs. Patients received either tocilizumab IV (8 mg/kg) or SQ (324 mg); within 24 hours, a second dose was administered to 52 of the 63 patients. Following tocilizumab, fevers resolved in all but one patient, and CRP, ferritin, and D-dimer levels declined. The PaO_2/FiO_2 ratio increased between admission (152 +/-53 mm Hg) and Day 7 (284 +/-116 mm Hg). No moderate or severe AEs attributable to tocilizumab were reported. Overall mortality was 11% (seven deaths among the 63 patients). No details were provided regarding the rate of secondary infections after tocilizumab use. The authors report an association of reduced mortality with earlier use of

Drug Name	FDA-Approved Indications	Pre-Clinical Data/Mechanism of Action/Rationale for Use in COVID-19	Clinical Data for COVID-19, SARS, or MERS (Find clinical trials on ClinicalTrials.gov)
Interleukin-6 Inhibitors, continued			
Tocilizumab, continued			tocilizumab, but provide no details regarding a comparison group or specify an a-priori comparison, which limits interpretation of this result.[32] • An uncontrolled, retrospective cohort study of 21 hospitalized COVID-19 patients who received tocilizumab reported improvement in oxygenation and systemic inflammation.[33] At study entry, of the 21 patients (mean age 56 years; range 25 to 88 years), 17 had severe disease and four had critical disease. All patients were febrile, had abnormal chest CT findings, and required oxygen supplementation (two required mechanical ventilation). Mean CRP level was 75 mg/L, mean IL-6 expression level was 153 pg/mL, mean D-dimer level was 0.80 μg/mL, and mean lymphocyte percentage was 15.5%. Eighteen patients were given tocilizumab IV infusion once, and within 12 hours, three patients received a second infusion for indication of fever. Following tocilizumab administration, fevers normalized, lymphocyte percentages improved, and CRP levels declined. By Day 5, oxygen requirements were reduced in 15 of 20 participants (75%). There were no serious AEs attributed to tocilizumab, and no concurrent bacterial, fungal, or viral infections were observed during the treatment. The interpretability of this retrospective case series is limited due to its small sample size and lack of control group.
Janus Kinase Inhibitor			
Baricitinib	Rheumatoid arthritis[34]	• JAK inhibitor • Inhibition of kinases that regulate endocytosis (AAK1 and GAK) • Baricitinib is predicted to interfere with SARS-CoV-2 receptor-mediated endocytosis in lung AT2 alveolar epithelial cells.[35]	• No clinical data for COVID-19, SARS, or MERS • Baricitinib plasma concentrations are predicted to potentially be sufficient for AAK1 inhibition when administered at labeled dose (for the FDA-approved indication).[35]

Key: AAK1 = AP2-associated protein kinase 1; AE = adverse event; ARDS = acute respiratory distress syndrome; ARV = antiretroviral; AT2 = alveolar type 2; AZM = azithromycin; CAR = chimeric antigen receptor; CRP = C-reactive protein; CT = computerized tomography; FDA = Food and Drug Administration; GAK = cyclin G-associated kinase; HCQ = hydroxychloroquine; IDMC = independent data monitoring committee; IFN = interferon; IL = interleukin; IV = intravenous; IVIG = intravenous immune globulin; LPV/r = lopinavir/ritonavir; JAK = Janus kinase inhibitor; MERS = Middle East respiratory syndrome; MERS-CoV = Middle East respiratory syndrome coronavirus; PI = protease inhibitor; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous

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Table 3b. Characteristics of Immune-Based Therapy Under Evaluation for Treatment of COVID-19

(Last updated June 11, 2020)

- The information in this table is derived from data on the use of these drugs and biologic products for FDA-approved indications or in investigational trials; it is supplemented with data on their use in patients with COVID-19 where available.
- The effective dosing of these agents for treatment of COVID-19 is unknown. Therefore, the doses listed below are primarily derived from FDA-approved indications or from clinical trials investigating therapies for COVID-19.
- There are limited or no data on dose modifications for patients with organ failure or those who require extracorporeal devices. Please refer to product labels, when available.
- Treatment-related AEs associated with immune-based therapy in patients with COVID-19 are not well defined. It is not known whether the frequency and severity of AEs in this population is similar to that in patient populations using these agents for FDA approved indications, especially in critically ill patients. Reported AEs of these drugs that are associated with long-term therapy (i.e., months to years) are not included in this table because treatment for COVID-19 is not long term. Please refer to product labels, when available.
- There are currently not enough data to determine whether certain medications can be safely coadministered with treatment for COVID-19. When using concomitant medications with similar toxicity profiles, consider additional safety monitoring.
- The potential additive, antagonistic, or synergistic effects and the safety of combination therapies for treatment of COVID-19 are unknown. Clinicians are encouraged to report AEs to the FDA *Medwatch* program.
- For drug interaction information, please refer to product labeling and visit the Liverpool COVID-19 Drug Interactions website.
- For information on drugs that prolong the QTc interval, please visit CredibleMeds.org.

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood Products					
COVID-19 Convalescent Plasma and SARS-CoV-2 Immune Globulins	Single or multiple transfusions based on patient response	• TRALI and TACO have been reported.[1] • Fever, allergic reactions ranging from urticaria to anaphylaxis (rare) • Transmission of infectious pathogens • Antibody-mediated enhancement of infection • Red cell alloimmunization	Monitor for transfusion-related reactions. Observe the patient and measure vital signs at baseline and during and after transfusion.	Drug products **should not be added** to the IV infusion line for the blood product.	• There are insufficient data to recommend either for or against the use of COVID-19 convalescent plasma or SARS-CoV-2 immune globulins for the treatment of COVID-19. • The FDA has provided guidance for the use of COVID-19 convalescent plasma under an emergency IND application. • The FDA has approved a national expanded access program for the use of convalescent plasma for the treatment of patients with COVID-19. Clinicians can refer to the National COVID-19 Convalescent Plasma Project website for more information. People who have fully recovered from COVID-19 for at least 2 weeks and are interested in donating plasma can contact their local blood donor or plasma collection center or refer to the American Red Cross website. • A list of clinical trials is available: Convalescent Plasma and Immune Globulin

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Blood Products, continued					
Non-SARS-CoV-2 Specific Intravenous Immune Globulin	Doses vary based on indication and formulation.	• Thrombotic events • Renal dysfunction and acute renal failure (more common with certain products) • Flu-like symptoms, dermatologic effects, arrhythmia, TRALI, anaphylaxis, aseptic meningitis, and hemolysis • AEs may be precipitated by high dose, rapid infusion, or underlying conditions, including IgA-deficiency. AEs may vary between formulations. • Consider the risks and benefits of the high-dose regimen in patients with increased risk of thrombosis, hemolysis, acute kidney injury, or volume overload.	• Observe the patient and measure vital signs at baseline and during and after infusion. • Discontinue if renal function deteriorates during treatment.	IVIG may interfere with immune response to certain vaccines.	• The Panel **recommends against** the use of non-SARS-CoV-2 specific IVIG for the treatment of COVID-19, except in a clinical trial **(AIII)**. This should not preclude the use of IVIG when otherwise indicated for treatment of complications that arise during COVID-19. • A list of clinical trials is available: Intravenous Immunoglobulin

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interferons					
Interferon Alfa	Peginterferon alfa-2a 180 mcg SQ once weekly for 2 weeks for MERS[2,3]	Flu-like symptoms (e.g., fever, fatigue, myalgia), injection site reactions, liver function abnormalities, decreased blood counts, worsening of depression, insomnia, irritability, nausea, vomiting, and hypertension[4]	• CBC with differential • LFTs (ALT); avoid if Child-Pugh Score >6 • Depression, psychiatric symptoms • Reduce dose in patients with CrCl <30 mL/min.	• Low potential for drug interactions • Inhibition of CYP1A2	• The Panel **recommends against** the use of IFN alfa, except in a clinical trial **(AIII)**. • For MERS, SQ formulation used in combination with ribavirin. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN; discontinue if accompanied by increase in bilirubin. • Reduce dose or discontinue if neutropenia or thrombocytopenia occur. • A list of clinical trials is available: Interferon
Interferon Beta	**IFN Beta-1a:** • 44 mcg SQ three times weekly[3] for MERS • Duration for COVID-19 unknown • SNG001 (this formulation delivered by nebulization is not approved in the United States). **IFN Beta-1b:** • 0.25 mg SQ every 48 hours for MERS[5] • Duration unknown	Flu-like symptoms (e.g., fever, fatigue, myalgia), leukopenia, neutropenia, thrombocytopenia, lymphopenia, increased liver enzymes (ALT > AST), injection site reactions, headache, hypertonia, pain, rash, and worsening of depression[6,7]	• LFTs • CBC with differential • Worsening CHF • Depression, suicidal ideation	Low potential for drug interactions	• The Panel **recommends against** use of IFN beta, except in a clinical trial **(AIII)**. • Use with caution with other hepatotoxic agents. • Reduce dose if ALT >5 times ULN. • Several products are available in the United States; doses differ between products. **IFN Beta-1a Products:** • Avonex, Rebif **IFN Beta-1b Products:** • Betaseron, Extavia • A list of clinical trials is available: Interferon

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-1 Inhibitor					
Anakinra	• Standard adult dose is 100 mg SQ once daily • Duration unknown	• Neutropenia (particularly in combination with other agents that can cause neutropenia) • Anaphylaxis • Headache, nausea, diarrhea, sinusitis, arthralgia, flu-like symptoms, and abdominal pain • Injection site reactions	• CBC • Renal function (reduce dose in patients with CrCl <30 mL/min)	Use with TNF-blocking agents **is not recommended** due to increased risk of infection.	• There are insufficient data for the Panel to recommend for or against the use of IL-1 inhibitors (e.g., anakinra) for the treatment of COVID-19. • A list of clinical trials is available: Anakinra
Interleukin-6 Inhibitors					
Sarilumab[8]	**Clinical Trial Dosing (See NCT04315298):** • 400 mg IV vs. placebo (single dose)[9] **Note:** The only FDA-approved sarilumab product is an SQ formulation.	• Neutropenia, thrombocytopenia • Gastrointestinal perforation • HSR • Increased ALT and AST • Hepatitis B reactivation • Infusion reaction possible	• Monitor for HSR • Monitor for infusion reaction • Neutrophils, platelets, liver function	• Elevated IL-6 may downregulate CYP enzymes; use of sarilumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• There are insufficient data for the Panel to recommend for or against the use of sarilumab for the treatment of COVID-19. • A list of clinical trials is available: Sarilumab
Siltuximab	• 11 mg/kg IV over 1 hour every 3 weeks for multicentric Castleman disease[10] • Dose and duration for COVID-19 unknown	• Infusion-related reaction • Gastrointestinal perforation • Neutropenia • Hypertension	• Hypersensitivity • Monitor for infusion reaction • Neutrophils	• Elevated IL-6 may downregulate CYP enzymes; use of siltuximab may lead to increased metabolism of drugs that are CYP450 substrates.	• There are insufficient data for the Panel to recommend for or against the use of siltuximab for the treatment of COVID-19. • May mask signs of acute inflammation (i.e., suppression of fever and CRP) • A list of clinical trials is available: Siltuximab

Drug Name	Dosing Regimen *There are no approved doses for the treatment of COVID-19. The doses listed here are for approved indications or from reported experiences or clinical trials.*	Adverse Effects	Monitoring Parameters	Drug-Drug Interaction Potential	Panel Recommendations, Comments, and Links to Clinical Trials
Interleukin-6 Inhibitors, continued					
Siltuximab, continued		• Dizziness • Rash • Pruritus • Hyperuricemia		• Effects on CYP450 may persist for weeks after therapy.	
Tocilizumab[11]	**Clinical Trial Dosing:** • 8 mg/kg IV once • Dose **should not exceed** 800 mg. • Dose may be repeated once, 12 hours later, if clinical symptoms worsen or show no improvement (see NCT04320615).	• Infusion-related reactions • HSR • Gastrointestinal perforation • Hepatotoxicity • Treatment-related changes in neutrophils, platelets, lipids, and LFTs • Hepatitis B reactivation	• Monitor for HSR • Monitor for infusion reactions • Neutrophils, platelets • LFTs	• Elevated IL-6 may downregulate CYP enzymes; use of tocilizumab may lead to increased metabolism of drugs that are CYP450 substrates. • Effects on CYP450 may persist for weeks after therapy.	• There are insufficient data for the Panel to recommend for or against the use of tocilizumab for the treatment of COVID-19. • SQ formulation **is not intended** for IV administration. • A list of clinical trials is available: Tocilizumab
Janus Kinase Inhibitor					
Baricitinib[12]	• 2 mg PO once daily for rheumatoid arthritis • Duration unknown	• Lymphoma and other malignancies • Thrombosis • Gastrointestinal perforation • Treatment-related changes in lymphocytes, neutrophils, hemoglobin, liver enzymes • Herpes simplex • Herpes zoster	• Treatment-related decreases in neutrophils, lymphocytes, and hemoglobin • Renal and hepatic function • Monitor for new infections	Dose modification is recommended when concurrently administering with a strong OAT3 inhibitor.	• The Panel **recommends against** the use of baricitinib, except in a clinical trial **(AIII)**. • **Not recommended** in patients with severe hepatic or renal impairment. • A list of clinical trials is available here: Baricitinib

Key: AE = adverse effect; ALT = alanine transaminase; AST = aspartate aminotransferase; CBC = complete blood count; CHF = congestive heart failure; CrCl = creatinine clearance; CRP = C-reactive protein; CYP = cytochrome P; FDA = Food and Drug Administration; HSR = hypersensitivity reaction; IFN = interferon; IgA = immunoglobulin A; IL-1 = interleukin-1; IL-6 = interleukin-6; IND = Investigational New Drug; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; MERS = Middle East respiratory syndrome; OAT = organic anion transporter; PO = orally; SARS = severe acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SQ = subcutaneous; TACO = transfusion-related circulatory overload; the Panel = the COVID-19 Treatment Guidelines Panel; TNF = tumor necrosis factor; TRALI = transfusion-related acute lung injury; ULN = upper limit of normal

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